MINI-REVIEW

Male Breast Carcinoma: Epidemiology, Risk Factors and Current Therapeutic Approaches

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Abstract

Male breast cancer is a very rare disease with an incidence of about 0.5–1% comparing with the one of female breast cancer but relatively little is known about its cause. Treatment strategies for breast cancer in males are derived from studies performed among females. The probable reasons behind the frequent, late diagnoses presented at stages III or IV might be the lack of awareness. The rarity of the disease precludes large prospective randomized clinical trials. This study reviews male breast cancer and its risk factors, recommendations for diagnosis and the management of patients with male breast cancer.

Key words: Male breast cancer - epidemiology - treatment - review.

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Introduction

Male breast cancer (MBC) is a very rare disease comparing with the one of female breast cancer (FBC) but relatively little is known about its cause. It has a peak incidence at 71 years of age, while the incidence for female breast cancer has two peaks, at 52 and 71 years, respectively. Men have a smaller amount of breast tissue than women but the factors that influence malignant changes in women operate quite in the same way in men as well. Male breast cancer has been described by some authors to behave like breast cancer in the postmenopausal women. Diagnostic and treatment strategies and recommendations have therefore major shortcomings compared to the same disease in females with early or metastatic breast cancer. Treatment strategies for male breast cancer are not based on data from randomized clinical studies. (Giordano et al., 2004; Rossman et al., 2007; Contractor et al., 2008; Anderson et al., 2010).

Risk Factors

Family history can affect the predisposition of male breast cancer. An estimated 15% of all MBC is familial. The BRCA2 gene, discovered in 1994, has been shown to be related to MBC. The life- time risk of MBC in BRCA2 carriers is estimated to be higher about the age of 70 years. BRCA2 is associated with most inherited breast and ovarian cancer in women and the link is less strong to MBC than the one to BRCA2. Other genetic mutations resulting in MBCinclude androgen receptor (AR) gene mutation , CYP 17 polymorphysm, CHEK2 mutation (Li Fraumeni syndrome), PTEN mutation (Cowden syndrome), and the Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) . A history of MBC is associated with a 30 fold increased risk on the contralateral side, which is much higher than the increase of 2 to 4-fold observed in women.(Meijers-Heijboer et al., 2002; Levy-Lahad et al., 2007; Lanitis et al., 2008; Mohamad et al., 2008; Daly et al., 2009; Ottini et al., 2009; Ottini et al., 2010; Taber Johansen et al., 2010).

Another risk factor is Klinefelter's syndrome. Among 3,518 patients with Klinefelter's syndrome 5 died of breast cancer. Increased oestradiol has been detected in the circulation of up to twice the upper normal limit. It is obvious that the chromosomal abnormality is likely to render the carrier prone to cancer but the effect we see in MBC may be brought about by hormonal changes. (Swerdlow et al., 2005; Contractor et al., 2008).

Moreover,the effect of increased prolactin level is interesting. A few cases in the literature describe the association between the MBC and pituitary prolactinoma. Owing to the stimulation by hyperprolactinaemia, the male breast tissue changes from premalignant to MBC. The risk of breast cancer in women with prolactinoma is not known (Forloni et al., 2001).

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Table 1. Risk Factors for Male Breast Cancer

History of BRCA-suggestive cancer, either in self or family
Known presence of BRCA mutation
Androgen receptor gene mutation
CYP 17 polymorphysm
CHEK2 mutation (Li-Fraumeni syndrome)
PTEN mutation (Cowden syndrome)
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)
Klinefelter syndrome
Exogenous oestrogen or anti-androgens therapy(prostate cancer), prolactine drugs (pituitary prolactinomas)
Occupational exposure (high temperature, low frequency magnetic fields)

There are some professions which are connected to MBC such as work places with high temperatures and low frequency magnetic fields (Brinton et al., 2008).

Prostate cancer is associated with MBC. Both are hormonal responsive tumours. According to several reports long term use of anti-androgens and oestrogens in the treatment of prostatic cancer has resulted in MBC (Dicker et al., 2003; Thellenberg et al., 2003; Coard et al., 2004;Chianakwalam et al., 2005). External radiation has been associated with a few cases of MBC, for the treatment of Hodgkin's disease (Cutuli et al., 2001). In summary, the risk factors associated with male breast cancer are shown in Table 1.

Clinical Presentation

Eighty five percent of MBCs present as a subareolar mass. Because of the unique anatomy of the male breast, the nipple has ulceration or discharge more often than in women.(Giordano et al.,2004). These conditions in men should always be investigated with biopsy (Ribeiro et al.,1996). Male breast cancer should be diagnosed with a combination of clinical examination, mammography and biopsy. The histopathology allows the determination of invasiveness and the appearance of the axillary lympnodes (Ribeiro et al.,1996).

In females about 90% of the tumors are pathologically characterized as ductal carcinomas. Breast cancers in males seem to resemble breast cancer in postmenopausal women as they have oestrogen (ER) and progesterone receptor (PR) positive as well as a low nuclear grade. These data are partly challenged by Cutuly et al review describing that 12–20% of male breast cancers are grade I, 54–58% grade II and 17–33% grade III.(Cutuli et al.,2007). In the same review the number of oestrogen and progesterone receptor positive patients was 75–92% and 54–77%. These data mimic the general receptor status findings in females with breast cancer. Breast cancer in males can not therefore automatically be categorized as low risk cancers (Cutuli et al., 2007).

However, in other studies the frequence of positive axillary lympnodes has been examined. Cutuli et al have detected 308 patients that from them only 44% had a node negative disease and 26% had four or more positive axillary nodes (Cutuli et al., 1995). Similar data have been presented by other authors with 43–53.5% of node negative patients in studies including 56–170 patients (Giordano et al., 2004; Macdonald et al., 2005).

Furthermore, genetic testing is recommended for men and women who are diagnosed with breast cancer and they appear to have a strong family history of cancers that they are consistent with BRCA mutations.(ASCO Working Group on Genetic Testing for Cancer Susceptibility, 2007).

Treatment Options

The fundamental treatment for male breast cancer is surgery (Contractor et al., 2008). The most common surgical procedure for males is modified radical mastectomy. The sentinel node diagnosis procedure has also been studied in male breast cancer patients. The incidence of positive sentinel nodes tended to be higher in males compared to females, 37% vs 22.3% (p=0.1) (Cimmino et al.,2004; Boughey et al., 2006). However, breast conserving surgery with and without radiotherapy as well as more radical surgical procedures have also been used (Cutuli et al., 2007). In locally advanced breast cancer, neoadjuvant therapies such as endocrine and/or chemotherapy should be applied to males.

The indications for post-operative radiotherapy are the involvement of the skin and/or pectoral muscle and areola, inadequate margins and metastatic spread to the axillary lymph nodes. (Contractor et al., 2008). Cutuli et al (1995) applied post-operative radiotherapy in about half of the patients in one study of 397 patients. Nine out of 190 patients experienced a local relapse received post-operative radiotherapy, while 21 local recurrences were observed in 183 patients who did not receive post-operative radiotherapy.

Furthermore, another study conducted among 43 patients showed that the group which was submitted to a postoperative radiation therapy, had less local relapse (1/10 vs 8/30) (Willsher et al., 1997). The same result was observed in four other reports for a total of 83 patients (Gennari et al., 2004) .These data should be seen with caution because the method of comparison was inaccurate. The conclusions drawn from these reports show a similar effect in reducing local recurrences by post-operative radiotherapy in males as for females in multiple randomized studies (Clarke et al., 2005).

Gennari et al claimed that men with tumor larger than 1 cm and/or all males with more than one positive axillary node should be submitted to post-operative radiotherapy. (Gennari et al., 2004). These radiotherapy recommendations which are aimed to increase local control and to improve overall survival, should be in balance with possible side effects of normal tissues (Hooning et al.,2007).

It is crucial the radiotherapy planning be accurate. This is to say that the radiation technique should be three dimensional to avoid radiation delivery to the heart/coronary arteries and other important vascular structures. The irradiated lung volume should also be minimized. The radiation dose should be the standard dose reported above for females, i.e. 2Gy per fraction in 25 fractions. Boost radiotherapy should also be considered for male patients with suboptimal surgical margins. Publications with relapse rates with or without radiotherapy are shown in Table 2.

Table 2. Studies Concerning Relapse Rates with or without Radiotherapy

Studies	Total Patients	RT	No RT
Cutuli et al (1995)	397	9/190	21/183
Macdonald et al (2005)	60	2/60	1/60
Willsher et al (1997)	40	1/10	8/30

Neoadjuvant Systemic Treatment

The presence of invasiveness and the degree of endocrine responsiveness are essential for the type of the neoadjuvant therapy. When tumors are inoperable due to tumour ulceration, tumor adhesion to or infiltration of surrounding tissues, advanced lymph node status, the situation and the treatment options should be discussed with patients.

In inoperative MBC the treatment option is the preoperative radiation therapy. This strategy has been studied in females and it has demonstrated that it offers similar survival rates as in the corresponding therapy which was given in the adjuvant setting (Bergh et al.,2001). Moreover, aromatase inhibitors and trastuzumab with Her-2/neu have also been subscribed in the preoperative setting in females in phase II randomized studies in combination with chemotherapy (Buzdar et al., 2005; Smith et al., 2005; Pant et al., 2008).

Consequently, the major advantage of neoadjuvant therapy is that more female patients can be offered breast-conserving surgery while it is not a motivation for most men with breast cancer. Another advantage of neoadjuvant therapy is that the effect of therapy can be seen directly and also that patients with a pathologic complete response have better outcomes.

To sum up, the strategies and findings of pre-operative therapy in females should also be used for males with breast cancer, applying the same principles and indications; despite the shortage of data from randomized studies (Buzdar et al., 2005; Smith et al.,2005).

Adjuvant Systemic Treatment

Adjuvant treatment of men with node-negative breast cancer should be carried-out based on the same principles as the ones for women with the node-negative breast cancer. There has been no evidence so far that response to treatment is governed by different principles in men and women. Tamoxifen should be still considered as the optimal anti-endocrine adjuvant treatment option for male patients with endocrine responsive disease. However, this treatment recommendation is not based on data from prospective randomized trial (Smith et al., 2005).

Ribeiro et. al in one study with 39 male breast cancer patients have indicated a 17% absolute improvement of survival to up 5 years (Ribeiro et al.,1996). However the results of this study are underestimated due to the fact that the men received tamoxifen for one or two years only with very good results while the data from the women show the same outcome in a period of 5 years (Nordenskjold et al., 2005).

The production of oestrogen by testicules is responsible for 20% of circulating estradiol (Handesman et al., 2001). The estradiol values are 3–4 times higher in older males, compared to the ones in postmenopausal females. Anastrozole given at 0.5 or 1.0mg for 10 days to 16-year old males reduced the estradiol values by about 50%, while the testosterone values are increased by 41–61% (Mauras et al., 2000). This is due to a feedback activation of the hypothalamus–hypophysis axis resulting in release of gonadotropins. Letrozole demonstrated a linear reduction of the estradiol values, a 2–3mg dose resulted in a 70–80% reduction of the estradiol values in males (Trunet et al.,1993).

We can claimed that the aromatase inhibitors may operate better, if the testicular function is down-regulated, either by a surgical or medical orchidectomy which is preferred as it is not irreversible one (Turner et al.,2000). We have more studies on the consequences of adjuvant chemotherapy on relapse rate and overall survival in females than in men (O'Malley et al.,2002). Males have been treated with different types of adjuvant regimens such as CMF (cyclophosphamide, methotrexate and 5-fluorouracil), with anthracycline- and also taxane-containing combinations.(Giordano et al.,2005) .Giordano et al. studied 156 males breast cancer patients, treated between 1944-2001 and they concluded that the use of anthracycline- and tamoxifen-based on adjuvant therapies improved disease freeand overall survival. In details, adjuvant chemotherapy for node-positive patients resulted in a hazard ratio of 0.78, which was not statistically significant. On the other hand, the overall survival for adjuvant anti-endocrine therapy resulted in a hazard ratio of 0.45 and this value was statistically significant (p=0.01). The above mentioned results should be interpreted with caution because they were based on historical controls with relatively few patients studied (Romond et al.,2005).

Relied on the experience in females and on non-randomized data from men, males with breast cancer should be offered adjuvant chemotherapy especially the ones with hormone receptor-negative disease. This is to say with tumors non-responsive to anti-endocrine treatment and also the ones expressing an uncertain condition as well. However, at the time of diagnosis males are in general older and thereby they have a higher possibility to have medical contraindications to receive conventional chemotherapy.

For males with HER2/neu amplified breast cancers especially for the ones with node positive disease, trastuzumab should be discussed and most probably offered, based on the randomized data from females (Smith et al., 2007). Adjuvant Trastuzumab has not been based on evidence yet; therefore its use must be considered under clinical evaluation.

Treatment of Metastatic Disease

The same procedure is applied in men with relapsed breast cancer as in women. In the past, male breast cancer has been treated by different ablative surgical procedures such as adrenalectomy, hypophysectomy and orchidectomy. These radical surgical procedures resulted in a 55–80% objective response rate (Giordano

et al.,2004; Zabolotny et al.,2005; Contractor et al.,2008). Nowadays, based on risk-benefit criteria, these ablative surgical treatments should be replaced by modern medical techniques.

Tamoxifen has remained the main anti-endocrine treatment modality for males with receptor positive breast cancer so far. What is more other anti-endocrine and endocrine therapies have also been applied such as aromatase inhibitors, androgens, anti-androgens, corticosteroids, high dose oestrogens and progestagenes (Giordano et al., 2004; Contractor et al.,2008). These agents should be used according to the response or the recurrence of the disease. Their replacement will lead to better response rate. (Giordano et al.,2004; Zabolotny et al.,2005; Nahleh et al.,2006; Contractor et al.,2008).

In males who are affected by biologically aggressive disease and with a negative receptor should be submitted to a systemic chemotherapy. (Gancberg et al.,2002).

Prognosis

Overall, prognostic factors for male breast cancer (MBC) are the same as in female breast cancer (FBC), the lymph node involvement being the most important among them. The survival after 5 and 10 years is 90% and 84% respectively in node-negative disease versus 65% and 44% for node-positive disease. (Fisher et al.,1975). The prognosis is worse if four or more lymph nodes are involved (10-year survival drops to 14%). The fact is that patients with MBC do worse than their female counterparts. (Donegan et al.,1998). This obvious is the direct cause of the older age, co-morbidity at presentation and shorter life expectancy in men. Disease-specific survival is about 10% higher than overall survival in MBC(Vetto et al., 1999; Rossman et al.,2007).

Conclusions

Breast cancer in males is a rare disease compared to women. Breast cancer in males has similar features as breast cancer in females. Males, however, are frequently diagnosed with more advanced stage of disease, with 42% of the patients diagnosed with stage III/IV breast cancers.

Neoadjuvant and adjuvant treatment should be applied in men as it is for women, based on the tumour stage and biologic charecteristics. The use of adjuvant therapies has improved the outcome, although randomized data do not exist. Local or loco-regional radiotherapy should be more broadly applied in males, mainly due to the more advanced stage at the time of diagnosis. The doses of radiotherapy are similar whith those in females. Owing to the thin chest wall the planning of radiotherapy should be accurate to protect the normal tissues such as the heart and the lung. No data exist for hypofractionation schedules because of the thin breast tissue in men. Male patients with metastatic disease should be treated as their counterparts, based on the site of metastases, tumour and clinical characteristics.

For the time being and in the near future, the only recommendation that could be made is to increase public awareness of male breast cancer, which ought to result in less advanced stage of disease at the time of diagnosis.

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